REMARKS

Responsive to the final Office action mailed July 22, 2002, and the Advisory Action mailed April 4, 2003, Applicant submits the above amendment with a Request for Continued Examination. Applicant further withdraws the non-entered amendments submitted in the reply to final Office action, filed January 22, 2003.

Claims 12-119 are pending in the application, claims 1-11 having been canceled by the above amendment and claims 12-119 added. The specification has been amended to replace or clarify references to EMBL ACCESSION NO:M92431 with references to SEQ ID NO:2. Applicant requests verification that the substitute sequence listing and sequence listing in computer-readable form, also filed with the reply to final Office action on January 22, 2003, was entered into the file. The enclosed declaration from the inventor, John E. N. Morten, replaces the previously submitted Declaration (filed January 22, 2003), and establishes that the sequence now designated SEQ ID NO:2 is identical to the sequence of EMBL ACCESSION NO:M92431 at the time the earliest priority application was filed (September 19, 1998). The amendments filed herewith replace all amendments filed in the reply to the final Office action of January 22, 2003. According to the Advisory action (mailing date of April 4, 2003), the Examiner did not enter the amendments filed in the response to the final Office action, and Applicants request that they now be withdrawn.

Support for the new claims can be found throughout the specification. For example, support for new claim 12 can be found, *e.g.*, on page 4, lines 7-22, and page 7, lines 10-15. Support for new claims 13, 67 and 93 can be found, *e.g.*, on page 8, lines 9-10. Support for new claims 14-22, 68-76 and 94-102 can be found, *e.g.*, on page 1, lines 4-7, and on page 2, lines 9-12. Support for new claims 23, 77 and 103 can be found, *e.g.*, on page 6, lines 19-20. Support for new claims 24-31, 78-91 and 104-117 can be found, *e.g.*, on page 4, lines 14-22. Support for new claims 32-48 can be found, *e.g.*, on page 10, lines 16-29. Support for new claims 49-65 can be found, *e.g.*, on page 11, lines 6-18. Support for new claim 66 can be found, *e.g.*, on page 3 lines 8-17. Support for new claims 92, 118 and 119 can be found, *e.g.*, on page 3, lines 8-16 and on page 9, lines 10-14. Further support for new claim 118 can be found, *e.g.*, on page 1, lines 4-

7, and on page 2, lines 9-12. Further support for new claim 119 can be found, *e.g.*, on page 4, lines 21-22. No new matter has been added.

35 U.S.C. §101 and 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1-4, 6 and 7 under 35 U.S.C. §101 and §112, first paragraph, because the invention allegedly "lacks a credible, substantial, specific or well-established utility" (final Office Action, p. 2) and because "one skilled in the art would not know how to use the claimed invention" (final Office Action, p. 4). Claims 1-4, 6 and 7 have been canceled.

New claims 12-65 are similar to the canceled claims in that they are directed to methods of evaluating a human as being at risk for a disease characterized by the misregulation of a Vascular Cell Adhesion Molecule-1 (VCAM-1) gene, and to allele-specific primers and probes for detecting one or more polymorphisms in a VCAM-1 nucleic acid. To the extent the rejection for lack of utility may be applied to these new claims, Applicant traverses.

VCAM-1 is a ligand for the α4 integrin receptors and is involved in a variety of cellular processes. For example, VCAM-1 has been implicated in T-cell proliferation, B-cell localization to germinal centers, hematopoietic progenitor cell localization in the bone marrow, angiogenesis, placental development, muscle development, and tumor cell metastasis (Specification, p. 2, lines 13-15). To facilitate its role in such varied processes, the VCAM-1 gene has a complex promoter that regulates the expression of the gene in the appropriate tissues at the appropriate times and at the appropriate levels.

Overexpression of the VCAM-1 gene is a hallmark of a variety of human inflammatory diseases including rheumatoid arthritis, multiple sclerosis, allergic asthma and atherosclerosis (Specification, p. 1, lines 26-28). Upregulation of VCAM-1 in response to inflammation occurs in vascular endothelial cells and is regulated by transcriptional activation thought to involve the transcription factor nuclear factor-κB (NF-κB) (Specification, p. 1, line 30- p. 2, line 2).

Even basal expression levels of VCAM-1 are regulated. For example VCAM-1 is normally expressed in low levels or is absent in endothelial cells, while VCAM-1 is

constitutively expressed on lymphoid dendritic cells, bone marrow fibroblasts, and certain macrophages (see Iademarco *et al.*, 1992; Ref. RR on PTO-1449 filed March 16, 2001). In addition, Iademarco *et al.* (*Proc. Natl. Acad. Sci. USA*, 90:3943-3947, 1993; ref. AQ submitted herewith) teach that the high basal expression of VCAM-1 in muscle cells is independent of cytokine activity, even while cytokines have been found to induce VCAM-1 expression *in vitro* in endothelial cells. Iademarco *et al.* (1992) report the identification of a silencer region at the 5′ end of the promoter, extending from nucleotide (nt) 540 to nt 1892 of the nucleotide sequence corresponding to EMBL ACCESSION NO:M92431. This silencer region was shown by Iademarco *et al.* (1992) to be responsible for the low basal expression level of VCAM-1 in endothelial cells. Five of the polymorphisms that are the subject of the present claims lie within the silencer region identified by Iademarco *et al.* (1992) (the sixth polymorphism is located upstream of the silencer region).

Since it is general knowledge in the art that the promoter region of a gene contains sequence elements that regulate gene expression, anyone having ordinary skill in the art would appreciate the potential of any of the polymorphisms to disrupt the regulated expression of VCAM-1, thereby leading to misexpression of VCAM-1 protein and subsequent disease in a human. The general understanding of the role of the promoter in the regulation of gene expression is illustrated by a quote from Iademarco *et al.* (1992). When Iademarco *et al.* began their studies to understand the mechanisms regulating VCAM-1 expression, they studied the promoter: "As a first step in determining how VCAM-1 expression is controlled at the molecular level, we have cloned and begun an analysis of the promoter for the VCAM-1 gene" (p. 16324, col. 1, of Iademarco *et al.* (1992); emphasis added).

Polymorphisms of the invention interrupt predicted consensus binding sites. Iademarco *et al.* (1992) identified nine potential transcription factor binding sites in the silencer region of the promoter. One of these (corresponding to nt 1462-1470 of SEQ ID NO:2; AAGTATGCA) includes a sequence that is identical to a binding site for TEF-1 (AGTATG; Jiang *et al., DNA Cell Biol.* 19:507-14, 2000; ref. AR submitted herewith), a tissue specific enhancer factor. This

6-nucleotide sequence includes the site of the VCAM-1 polymorphism located at nt 1467 of SEQ ID NO:2 (AGTA(T/C)G).

The Examiner seems to be concerned with the Applicant's reference to Jiang *et al.* because it was published after the filing date of the instant application. In the Advisory action, the Examiner states:

> Applicants cite post filing date art to show that the polymorphism at position 1467 is within a TEF-1 binding site. However the specification as originally filed does not indicate that this polymorphism is within the TEF-1 binding site and does not indicate how the presence of this polymorphism alters the activity of the promoter.

Applicant points out that the "post filing date" art (Jiang *et al.,* 2000) was cited merely to show that the sequence surrounding and including the polymorphism site at nt 1467 is identical to a sequence that was later demonstrated to be bound by TEF-1. However, this promoter was previously identified as a TEF-1 consensus binding site in Iademarco *et al.* (1992), which was published well before the filing date of the instant application and in fact was cited in the information disclosure statement as reference RR, filed on March 16, 2001. The Jiang *et al.* reference was cited in the response to the final Office action to demonstrate that Iademarco *et al.* (1992)'s prediction that the capability of the VCAM-1 promoter sequence incuding nt 1467 to bind to TEF-1 was correct.

Iademarco *et al.* (1992) also reported two potential binding sites for the ets proto-oncogene protein factors and three potential binding sites for octamer transcription factors in the silencer region of the VCAM-1 promoter. Iademarco *et al.* (1993) remarks that there are at least ten other sites in this region that show similarity to octamer binding sequences. In addition, and as acknowledged by the Examiner on page 2 of the final Office action, Applicant points out other specific known transcription factor binding sites that are created or interrupted by the presently claimed polymorphisms. These are mentioned in the specification at page 6, lines 26-31, and at page 15, in the first table.

The complexity of the VCAM-1 promoter is critical for its role in tissue-specific expression (the low basal expression of VCAM-1 in endothelial cells contrasts with the high basal level of expression in other cell types), and upregulation of the promoter is known to occur in response to the inflammation that is associated with the human inflammatory diseases mentioned above. The significant role of the promoter in regulated VCAM-1 expression is evidence of a specific, substantial, and credible utility, as well as a well-established utility, for the methods and compositions of the new claims and particularly for the new claims 12-65 in the instant application. For example, and as pointed out in the specification, detection of the VCAM-1 polymorphisms by the methods of the invention can be used to identify individuals at risk for developing a VCAM-1 mediated disease, such as an inflammatory disease (Specification, p. 3, lines 14-17). The primers and probes of new claims 32-65 are useful for identifying the presence of a polymorphism in an individual in accordance with the methods of the invention.

The methods and compositions of the new claims, and of new claims 12-65 in particular, have specific and substantial utility, because the polymorphisms fall in the promoter of the gene and as discussed above, sequence elements in the promoter regulate a complex pattern of gene expression. Therefore, detection of one or more of the described polymorphisms predicts misregulation of VCAM-1 gene expression. This applies to basal expression levels as well as upregulated expression in response to external factors, such as inflammatory agents. MPEP 2107.01(I) states: "...the situation where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition...[is] sufficient to identify a specific utility of the invention." Further, "A 'substantial utility' defines a 'real world' use." The use of the methods and compositions of the new claims to identify an individual at risk for a VCAM-mediated condition is a "real world" use, and thus the methods and compositions of the new claims have substantial utility.

Applicant's proposed utility is also credible. MPEP 2107.02 states that "[a]n assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion." The Examiner has not established how the logic underlying Applicant's assertion of utility is

"seriously flawed," nor precisely which facts upon which the assertion is based "are inconsistent with the logic underlying the assertion." Accordingly, Applicant submits that the asserted utility is credible.

The Examiner notes in the Advisory action that the rejections under §§101 and 112, first paragraph, are not based on the utility of VCAM-1 or the utility of the VCAM-1 promoter. According to the Examiner, the rejections are based on the utility of the claimed nucleic acids containing polymorphisms in the VCAM-1 promoter. The Examiner is concerned that the polymorphisms of the claimed nucleic acids might not alter the wildtype expression patterns described above. She also opines in the Advisory action that for a polymorphism in the VCAM-1 promoter to be useful in the diagnosis of an inflammatory disease or for determining the risk of inflammatory disease, a polymorphism would have to have the property of increasing expression of VCAM-1.

Applicant respectfully disagrees with the Examiner's reasoning that the polymorphisms are not useful unless the presence of the polymorphisms has been shown to lead to increased expression of VCAM-1. The polymorphisms are in a gene whose overexpression is known to occur in the human inflammatory diseases mentioned above. In addition, the polymorphisms are in a region of the gene (the promoter) known to be a key regulator of expression levels. One of ordinary skill in the art will appreciate the mechanism by which promoters operate to regulate gene expression. The Discussion section of Iademarco *et al.* (1993) provides an excellent summary of the varied activity of the VCAM-1 promoter (see Table 1, for example). The octamer elements in the VCAM-1 promoter down-regulate expression in both endothelial and muscle tissue. The NF-κB sites upregulate VCAM-1 gene expression in the two cell types, and a position-specific enhancer upregulates expression in muscle tissue. Given the varied activity of the promoter elements in the VCAM-1 gene, the polymorphisms in the claimed nucleic acids would at the very least flag an individual as being one who is at risk for a VCAM-1-mediated disease.

Furthermore, and as noted in Applicant's response to the final Office action, MPEP §2107.01 states that "any reasonable use that an applicant has identified for the invention

that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial utility.'" In addition, the U.S. Patent and Trademark Office "Utility Examination Guidelines" (Fed. Reg. Vol. 66, No. 4 (January 5, 2001)) state, "An invention has a well-established utility...if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention..." Applicant maintains that a person of ordinary skill in the art would indeed immediately appreciate the usefulness of detecting at least one of the cited nucleotide polymorphisms in the promoter of the VCAM-1 gene for the purpose of diagnosing an inflammatory disease or for determining a level of risk for an inflammatory disease in a human.

In view of the foregoing, Applicant asserts that the methods and nucleic acids of the new claims have utility and are enabled by the disclosure of the specification.

35 U.S.C. §112, second paragraph

Claims 1-4, 6 and 7 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. The claims were rejected as being indefinite over the recitation of "EMBL ACCESSION NO:M92431" in the specification and in the claims. The Examiner recommended using a numbering scheme relative to the specific nucleotide sequence provided in a sequence listing (final Office action, page 5).

In response to the final Office action and the Examiner's suggestion, the specification has been amended to replace references to "EMBL ACCESSION NO:M92431" with "SEQ ID NO:2." A sequence listing (including a paper copy and copy of verified statement) was filed on January 22, 2003, with the response to the final Office action to satisfy the requirements for nucleotide sequence disclosures under 37 C.F.R. §§1.821-1.825. In addition, Applicant submitted a first declaration from the inventor, John E. N. Morten, establishing that the sequence now designated SEQ ID NO:2 is identical to the sequence of EMBL ACCESSION NO:M92431 at the time the earliest priority application was filed (September 19, 1998).

As indicated in the Advisory Action, the Examiner did not enter the first proposed amendment because

> [t]he amendment...raises new issues under 35 U.S.C. 112 first paragraph (new matter) because while the declaration establishes that an EMBL sequence attached as exhibit A is identical to the EMBL sequence that existed as of September 9, 1998, the declaration does not establish that SEQ ID NO:2 is identical to the sequence that existed as EMBL Accession No:M92431 as of September 9, 1998 (page 2, first paragraph of the Advisory Action).

Applicant thanks the Examiner for a courteous telephone interview with Applicant's representative, Dr. Allyson Hatton, on July 15, 2003. In the course of the interview, the Examiner agreed to consider a second declaration from the inventor (submitted herewith as Appendix B). The second declaration addresses the issue raised in the Advisory Action by adding the language underlined below:

> I hereby declare that the sequence represented by Exhibit A is identical to the sequence of EMBL ACCESSION NO:M92431 that existed at the time the earliest priority application was filed (September 19, 1998), and is also identical to the sequence referred to as SEQ ID NO:2 throughout the specification of the instant application. Accordingly, the sequence referred to as SEQ ID NO:2 throughout the specification is identical to the sequence of EMBL ACCESSION NO:M92431 that existed at the time the earliest priority application was filed.

Claims 1-4, 6 and 7 have been canceled, and the new claims refer to "SEQ ID NO:2" instead of EMBL ACCESSION NO:M92431. Applicant believes the second declaration overcomes the §112, second paragraph, rejection of the new claims, and respectfully requests that the rejection be withdrawn.

Enclosed is a $2460 check for Request for Continued Examination fee and a $1970 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-277001.

Respectfully submitted,

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Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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